J. Pharm. Res. 2021;20(3):30–37

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

RESEARCH ARTICLE

Comparative *In Vitro* Quality Evaluation of Brands of Propranolol Tablet Marketed in Okada, Edo State, Nigeria.

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ARTICLE INFO

Article history:
Received 21.05.2021
Revised 19.06.2021
Accepted 28.06.2021
Published 25.11.2021

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https://doi.org/10.54839/v20i3.ms21055

ABSTRACT

Propranolol, a beta-blocker is used in the management of cardiovascular conditions such as irregular heart rate and high blood pressure. The study was carried out to examine the *in vitro* quality control tests for seven brands of propranolol hydrochloride 40 mg tablet formulation, sold in retail pharmacies in Okada, EdoState, Nigeria.

The parameters determined were identification, weight variation, friability, hardness, disintegration, dissolution rate, and assay of the tablets. The tablets were evaluated for conformity with British Pharmacopoeia (BP) standards.

Results obtained showed tablet weight in the range of 155.6 ±3.2 mg to 348.2 ±2.0mg, hardness ranged from 1.03 ±0.17to 10.70 ±0.90 kg/cm^2, friability of < 1 % except for one brand, disintegration time of 1.37 ±0.15 to 18.05 ±2.88 min whereby two brands are uncoated tablets and assay of 90.07 ±1.15 to 102 ±1.62% with one brand deviating from the specified limit. The seven batches also released more than 80% of their drug content within 30min. Analysis of similarity factor revealed that all brands but PN-7 can be interchangeable with PN-1 in terms of dissolution profile.

The study showed that propranolol samples examined passed all the Pharmacopoeial tests for satisfactory quality exceptPN-6 which did not comply with most of the Pharmacopoeial specifications. Thus, not all brands can be used interchangeably in clinical practice.

Keywords: Propranolol; Quality Control; Dissolution; Pharmacopoeial specifications

INTRODUCTION

The importance of the quality, efficacy, and safety of pharmaceutical products to safeguard public health cannot be over-emphasized. The world at large and more especially the third world countries are facing the danger of substandard, fake, or adulterated drug, treatment failure, and drug toxicity as well as other adverse health implications arising from the circulation of unwholesome drug products. The World Health Organization (WHO) has posited that about 10 % of the world's pharmaceutical trade in developing countries consists of fake or substandard products[1,2] while up to 25% of all drugs consumed in poor resource economies are alleged to be counterfeit or substandard.[3]

According to the WHO, counterfeit medicines (either branded or generics) are medicines that are deliberately and fraudulently mislabeled concerning their identity and/or source. Counterfeit medicines are regarded as medicines with either correct ingredients; wrong ingredients, without active ingredients, with incorrect amounts of active ingredients, or with fake packaging.[4] Substandard medicines are defined as products whose composition and ingredients do not meet the correct scientific specifications and are consequently ineffective and often dangerous to the patient. Distribution of spurious medicines and use of counterfeit medicines could cause a loss of confidence in health systems and healthcare providers.[5]

With the increase in demand for pharmaceutical products, comes the production of different categories of these products, and also diversity in brands. It has therefore become a necessity to keep the quality of pharmaceutical products in constant check, especially those that have already found their way to the market, ready for patients' consumption. Comparative analysis of the different available brands to the official standard would be an effective measure to ascertain the quality of these products, ensuring that

they meet required specifications and to detect sub-standard products.

Substandard medicines are a major public health threat in Africa and this affects all demographics of patients. The WHO estimates that over 280,000 children die annually because of taking counterfeit or substandard medicines as treatment for disease conditions like pneumonia and malaria in sub-Saharan Africa.[6] When counterfeit or substandard medicines are consumed, they can prolong illness and even cause more deleterious complications, thus constant post-market surveillance of drugs already in the market becomes imperative.

Propranolol Figure 1 is a beta-blocker drug used in the management of high blood pressure, irregular heart rate, thyrotoxicosis, capillary hemangiomas, performance anxiety, and essential tremors. It is used to prevent migraine headaches, and to prevent further heart problems in those with angina or previous heart attacks.[7]

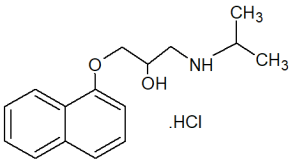

Fig. 1: Structure of propranolol hydrochloride[8]

Propranolol is chemically known as (2RS)-1-[(1-Methylethyl)amino]-3-(naphthalen-1-yloxy)propan-2-ol hydrochloride[8]. It has a molar mass of 259.34 g/mol and a melting point of 96 °C (205 °F). Pharmacokinetic properties include bioavailability of 26%, protein binding of 90%. Propranolol is metabolized in the liver extensively by CYP1A2, 2D6; minimally by CYP2C19, 3A4, having metabolites which include; N-desisopropylpropranolol, 4'-hydroxypropanolol. It has an elimination half-life of 4–5 hours and is excreted by the kidney (<1%).

It is a competitive antagonist of beta-1-adrenergic receptors in the heart.[9] It competes with sympathomimetic neurotransmitters for binding to receptors, which inhibits sympathetic stimulation of the heart.Its primary indication is the treatment and prophylaxis of sinus ventricular tachycardia. It is well tolerated by infants up to 4 mg/kg per day but requires weight-based dose adjustments to maintain the effect. Propranolol is the most widely explored β-blocking agent even in children,[10] thus there is a need for continuous monitoring of the quality of available brands to the consumers.

Studies reveal that several methods have been employed in the analysis of propranolol in bulk form as well as formulated tablets. These include Gas chromatography,[11] HPLC,[12] Capillary Electrophoresis using benzylamine as internal standard,[13] Thin layer Chromatography,[14] Electrochemical analysis,[15] Spectrofluorimetry,[16] and UV spectrophotometry[17] which is the BP official method.

The objective of this study was to assess the quality of different brands of propranolol 40 mg tablet commercially available in Okada township of Edo State, Nigeria, using compendia procedures found in the British Pharmacopoeia.

EXPERIMENTAL

Drugs and Chemicals

Propranolol powder was purchased from AKScientific, California. Seven brands of propranolol tablets were purchased from retail pharmacy shops in Okada town of Edo State, Nigeria. The samples were properly checked for their National Agency for Food and Drug Administration and Control (NAFDAC) registration numbers, batch numbers, production, and expiry dates. They were randomly designated as PN-1, PN-2, PN-3 up till PN-7. All other chemicals were of analytical grade and include sodium hydroxide, anhydrous sodium sulfate, methanol, ether.

Instruments

Instruments used in the study were weighing balance (Mettler Toledo), Hardness Tester (Mosanto, UK), Friability test apparatus (Campbell FTA-20 Single drum), Disintegration Test Apparatus (Esico International, India), M530 FTIR Spectrophotometer (Buck Scientific), and UV-visible spectrophotometer (Cecil CE 2000 series).

Determination of Uniformity of Weight

Twenty tablets from each of the brands were weighed individually with an analytical weighing balance. The average weights for each brand as well as the percentage deviation from the mean value were obtained.

Identification test

The identification tests used for propranolol tablets in this study are indicated in the British Pharmacopoeia (BP) 2017 as found below:

Ten tablets of each brand were selected at random and powdered. The quantity of powdered tablet containing 0.1 g propranolol was suspended in 20 mL of water and filtered; the filtrate was made alkaline with 1 M sodium hydroxide, extracted three times each with 10 ml of ether. The combined extract was washed with water until it is free from alkali and dried with anhydrous sodium sulphate. It was then filtered and evaporated to dryness. The residue was dried at 50°C for 1 hour and the infrared spectrum of each sample was determined. The melting point of the dried residue was also determined as required by the BP.[17]

Fourier-Transform Infrared Spectroscopy (FTIR)

FTIR spectra were obtained by using an FTIR spectrometer. The samples were mixed thoroughly with potassium bromide (KBr) in a Sample to KBr ratio of about 1:5 respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Scans were obtained at a resolution of 4 cm^{-1},from 4,000 to 300 cm^{-1}.

Hardness test

The crushing strength was determined with a tablet hardness tester. Five tablets were randomly selected from each brand and the pressure at which each tablet was crushed was recorded.

Friability test

Twenty tablets from each of the brands were weighed and placed in the friabilator and then operated at 25 rpm for 4 min. The tablets were then de dusted and weighed. The difference in the two weights was used to calculate friability by using the following formula[18]:

$$Friability = \frac{Iw - Fw}{Iw} x\ 100\%$$

where *Iw* is the total initial weight of the tablets and *Fw*is the total final weight of the tablets

Disintegration test

Six tablets of each brand were used for the test in distilled water at 37 °C with disintegration test apparatus employing plastic discs. The disintegration time was taken as the time when no particles remained in the basket of the tester.

Preparation of stock solution of propranolol

A stock solution (100 mL) of 5000 μg/mL was prepared by dissolving 0.5 g of propranolol in phosphate buffer, pH 6.8, and made up to the marked volume with the same solvent. Then 10 mL from this was diluted with phosphate buffer at pH 6.8 and finally, the volume was adjusted up to 100 mL with the same solvent. The resulting solution is called the stock solution of 500μg/mL. The stock solution was then diluted to the desired strength by phosphate buffer pH 6.8.

Preparation of Calibration Curve

Serial diluted solutions of 10, 20, 30, 40, 50, 60,70,80, 90, 100 μg/mL of propranolol were prepared from the stock solution (500 μg/mL) with phosphate bufferpH 6.8. The absorbances were taken at 290 nm using a UV-Visible spectrophotometer. A plot of absorbance versus concentration of propranolol was made from which the regression equation was calculated.

Assay

The chemical assay test for each brand of propranolol was carried out as stated in the BP[17]. The quantity of powdered tablets containing 20 mg propranolol hydrochloride was shaken with 20 mL of water for 10 minutes. Fifty mL of methanol was added and the mixture was shaken for another 10 minutes, sufficient methanol was then added to make 100 mL and it was filtered. Samples were suitably diluted and analyzed by UV spectrophotometry at a wavelength of 290 nm. Determination of propranolol hydrochloride was carried out in triplicate for each brand of tablet using the calibration curve conducted with the standard propranolol.

Dissolution test

The dissolution rate test was carried out using the USP apparatus 1 (basket method) in 6 replicates of each brand. The dissolution medium was 900 mL of phosphate buffer at pH 6.8 which was maintained at 37.0±0.5°C. In all the experiments, 5 ml of dissolution sample was withdrawn at 0, 10, 15, 30, 45, and 60 min and replaced with equal volume to maintain sink condition. Samples were filtered and assayed by UV-VIS spectrophotometer at 290 nm. The concentration of each sample was determined from a calibration curve obtained from standard samples of propranolol. The percent dissolutions were computed.

Analysis of similarity factor

Similarity factor (f_2) has been adopted by the United States Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products to compare dissolution profiles.[18,19] The dissolution profiles were analyzed by a mathematical model, similarity factor (f_2). Mean dissolution values were employed to estimate the similarity factor (f_2). A factor value of 50 or greater (50-100) ensures the sameness or equivalence of the two products. The equation below was used to calculate similarity factor (f_2):

$$f_2 = 50 \bullet \log \left\{ \left[1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \bullet 100 \right\}$$

Where n is the number of time points, R_t is the dissolution value of the reference product at a time 't', and T_t is the dissolution value for the test product at a time.

RESULTS

Description of sample tablets

Each product was found to have been properly strip packed and labeled with the names of the active ingredient, strength, and expiry date. The packets containing the strip packs also had the product name, strength, pack size, batch number, NAFDAC registration, expiry date, and Manufacturer's

name and address boldly written. As shown in Table 1 Table 1, all propranolol tablets collected and investigated were within their shelf lives.

Uniformity of weight

Weight variation or uniformity of the propranolol tablets are shown in Table 2. It was observed that all tablet brands had a coefficient of variance values of < 5 % except PN-6 with a percentage deviation of 7.6%. Thus, tablets from all the samples tested apart from PN-6 can bead judged to have passed the uniformity of weight test for uncoated tablets as stipulated by the British Pharmacopoeia.[17]

Identification Test

The melting point of the residue obtained after samples of each brand of the powdered tablet was suspended in water, made alkaline with NaOH, extracted with ether, and filtered was determined. The result obtained is stated in Table 2. The BP 17 states that the melting point for the residue of propranolol should be about 94^{o}C.

Furthermore, the infrared spectra of the residue of each brand were obtained and spectra are presented in Fig. 2-8. Some functional groups present in propranolol, confirmed by their IR absorption frequency ranges, intensity, and the frequency are presented in Table 3. The spectra of each sample tallies with normal frequency ranges.

Friability Test

The friabilitytest results for the sample brands are shown in Table 2. All the sample brands except PN-5 (with 1.52 % friability) gave a percentage friability of less than 1 % and thus passed the friability test.

Hardness Test

Hardness test determined for the brands of tablet range from 1.03±0.17Kg/cm^2 (PN-6) to 10.70±0.9Kg/cm^2(PN-7) as reported in Table 2. Hence the tablets of all brands except PN-5 and PN-6 were satisfactory for hardness based on the BP specification of 4-10 Kg/cm^2.

Disintegration Test

All the brands complied with the compendial specifications for disintegration. The BP specification is that uncoated tablets should disintegrate within 15 min and film coated in 30 min while USP specifies that uncoated and film coated tablets should disintegrate within 30 min. All the brands were uncoated tablets while brands PN-1 and PN-2 were film coated. The disintegration time details are as stated in Table 2.

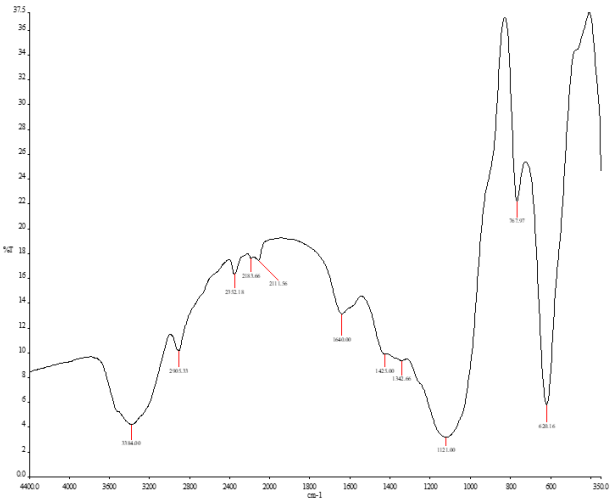

Fig. 2: FTIR spectrum of PN-1

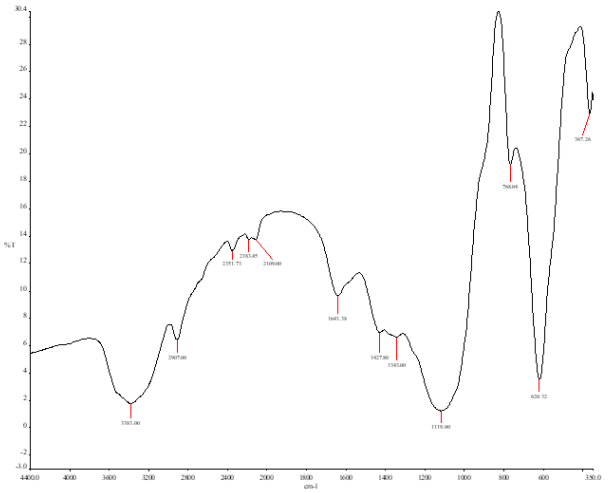

Fig. 3: FTIR spectrum of PN-2

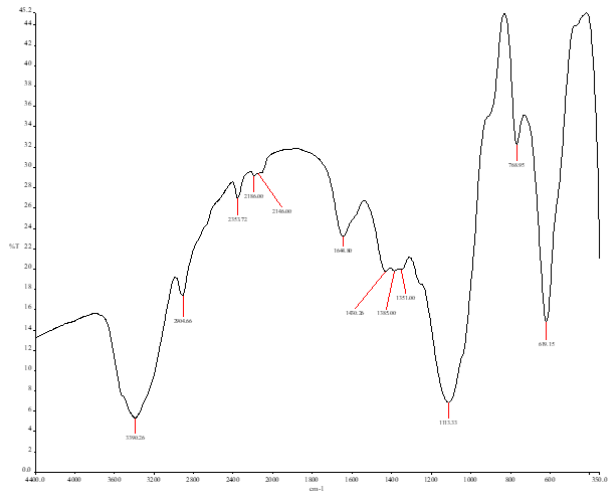

Fig. 4: FTIR spectrum of PN-3

Table 1: Description of different brands of propranolol tablets

Sample Code	Country of Origin	Shape	Color	Scoring	Coating	Batch No.	Expiry Date	NAFDAC Reg. No.
PN-1	United Kingdom	Circular	Pink	Scored	Film coated	85812-U	05/2020	NIL
PN-2	United Kingdom	Circular	Pink	Scored	Film coated	PB 1022	02/2020	NIL
PN-3	Nigeria	Circular	Pink	Scored	Uncoated	0032N-0718	09/2021	04-5733
PN-4	India	Circular	Pink	Not scored	Uncoated	XT9f030	05/2022	B4-6323
PN-5	India	Circular	White	Scored	Uncoated	18176801	11/2021	B4-8990
PN-6	India	Circular	Pink	Scored	Uncoated	T25018	06/2021	04-6513
PN-7	India	Circular	Pink	Not scored	Uncoated	F50810	11/2021	B4-7842

NAFDAC - National Agency for Food and Drugs Administration and Control; Reg.- registration

Table 2: A summary of the quality control test undertaken on the brands of propranolol.

Sample Code	Melting point range (°C)	MeanWeight (mg)	% Deviation from mean weight	Average Hardness Test±SD (Kg/cm^2)	Friability (%)	Disintegration Time±SD(min)	Assay±SD (%)
PN-1	96-98	165.4	±3.6	6.46 ±0.40	0.24	15.23±1.34	102.0±1.62
PN-2	94-97	155.6	±3.2	7.46±1.25	0.21	18.05±2.88	98.36±1.57
PN-3	95-99	164.0	±4.3	4.54±0.55	0.41	3.48±0.50	95.75±1.48
PN-4	95-97	338.0	±3.2	6.71±0.42	0.45	11.60±0.00	97.69±0.93
PN-5	93-95	348.2	±2.0	1.50±0.60	1.52	14.40±3.81	95.3±0.86
PN-6	96-99	185.4	±7.6	1.03±0.17	0.52	1.37±0.15	90.07±1.15
PN-7	95-98	214.1	±3.7	10.70±0.9	0.23	5.65±0.87	100.3±1.08

Calibration curve equation: $y = 0.0063x + 0.0733$, $R^2 = 0.9902$

Table 3: Frequency readings obtained from the different spectra and ranges for different functional groups.

Functional group	IR frequency ranges (cm^{-1})	Assignments (Intensity)	Frequencies from sample spectrum (cm^{-1})						
			PN-1	PN-2	PN-3	PN-4	PN-5	PN-6	PN-7
Alcohol (O-H)	3200-3600	O-H stretching (strong)	3384.0	3383.00	3390.3	3413.2	3269.1	3271.3	3388.5
Ether (C-O-C)	1050-1250	C-O-C stretching (strong)	1121.0	1119.00	1113.3	1126.4	1095.0	1121.4	1128.3
2° Amine (C-NH-C)	1580-1650	N-H bending (medium)	1640.0	1641.38	1644.8	1597.0	1606.2	1638.4	1644.9
Naphthyl ring (mono-substituted	730 - 770	C-H out of plane bending (strong)	767.9	768.04	768.95	755.8	760.2	728.1	767.9

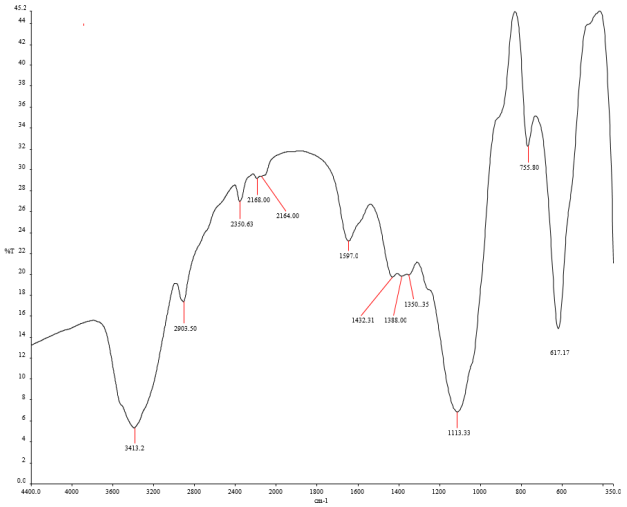

Fig. 5: FTIR spectrum of PN-4

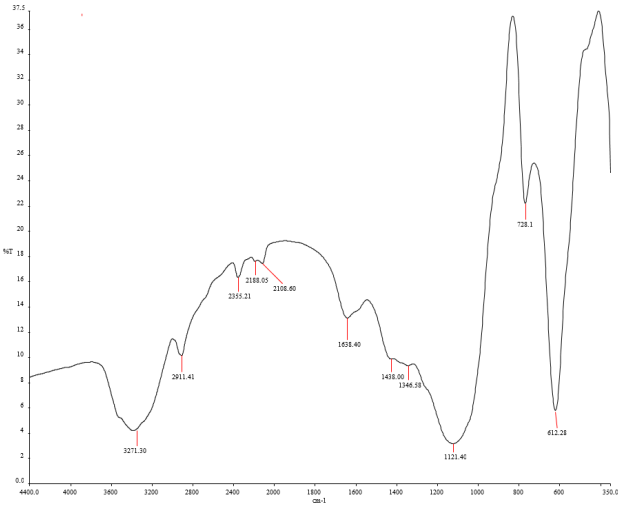

Fig. 7: FTIR spectrum of PN-6

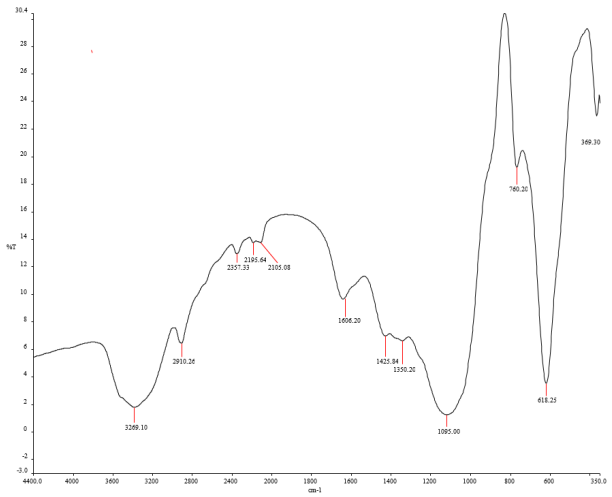

Fig. 6: FTIR spectrum of PN-5

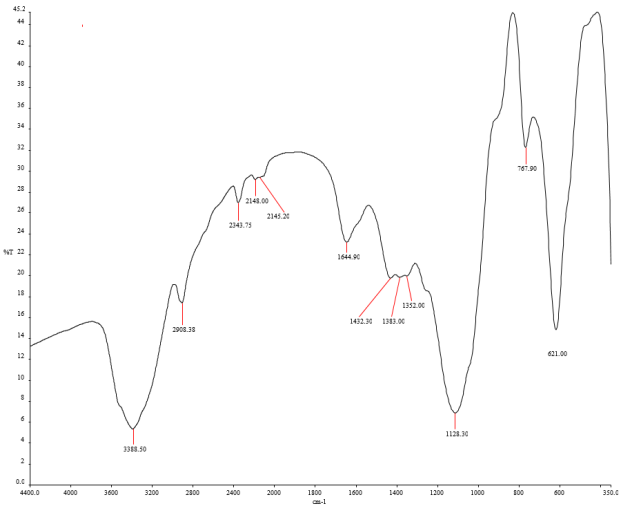

Fig. 8: FTIR spectrum of PN-7

Assay results

The results showing the content of active pharmaceutical ingredients using UV spectrophotometric method are shown in Table 2. All the tablet batches complied with the British Pharmacopoeia set the limit for propranolol hydrochloride tablet which states that such tablets should contain not less than 92.5 % or more than 107.5 % of the label claim[17]. However, PN-6 with a percentage content of 90.07±1.15% did not pass the assay test.

Dissolution Test

The USP[20] and BP[17] specify that the amount of drug released should not be less than 80% of the labeled amount at 30 min. Findings of this study are presented in Table 4.

All seven brands complied with the USP and BP as shown in Figure 9 and the release profile is almost super imposable. Thus, all the batches passed the dissolution test and their active pharmaceutical ingredient would be readily bioavailable for absorption when ingested. The table showed the percentage of drug dissolved from each brand of the sample drug.

Analysis of similarity factor

Two dissolution profiles are considered similar and bioequivalent, if f2 is between 50 and 10019. A T90% of 30 minutes is satisfactory and is an excellent goal[21]. In this study, parameters like T50%, T75%, T90% and f2 were derived from the dissolution profiles of the different brands. Table 5 showed the f2 values of different brands in respect of

Table 4: Mean percent dissolution of different brands of propranolol tablets.

Time (mins)	PN 1	PN 2	PN 3	PN 4	PN 5	PN 6	PN 7
0	0	0	0	0	0	0	0
10	52.3 ± 1.6	64.8 ± 1.93	77.5 ± 2.39	56.43 ± 1.69	67.11 ± 1.53	69.49 ± 1.05	72.87 ± 1.72
15	85.03 ±1.06	78.97 ± 1. 48	86.9 ± 1.98	81.44 ± 1.76	79.41 ± 1.08	85.04 ± 0.93	85.43 ± 1.65
30	90.56 ±0.93	88.29 ± 1.19	95.84 ± 1. 58	86.4 ± 1.25	86.05 ± 0.91	91.25± 0.81	89.72 ± 0.98
45	93.60 ± 0.89	97.05 ± 0.83	98.5 ± 1.27	91.7 ± 0.80	93.74 ± 0.83	95.77 ± 0.69	99.01 ± 0.80
60	102.3 ± 0.67	105.57 ±0.72	99.78 ± 0.85	95.08 ± 0.72	98.62 ±0.71	99.72 ± 0. 55	101.23 ± 0.74

Table 5: T50%, T75%, T90%and f_2 values of different brands of propranolol tablets.

Sample Code	T50%	T75%	T90%	Similarity Factor (f_2)
PN-1	< 10 min	< 10 min	< 30 min	
PN-2	<15 min	<45 min	<60 min	65.19
PN-3	<15 min	<45 min	<60 min	52.28
PN-4	<15 min	<45 min	<60 min	82.85
PN-5	<15 min	<45 min	<60 min	99.86
PN-6	<15 min	<45 min	<60 min	79.51
PN-7	<15 min	<45 min	<60 min	48.42

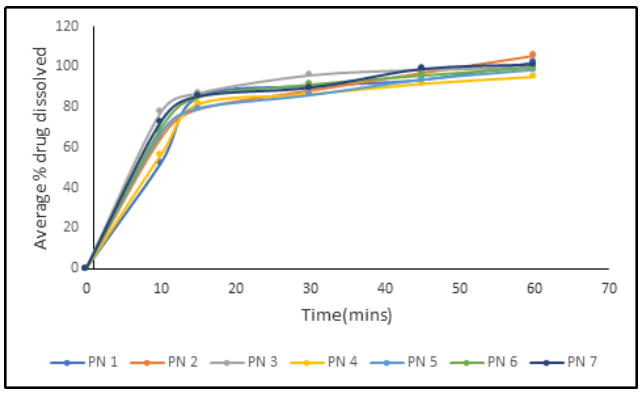

Fig. 9: Dissolution rate profile of brands of propranolol hydrochloride tablet

brand PN-1.

DISCUSSION

All the tablets examined were circular, pink in color, and scored except PN-4 and PN-7 which were not scored. Tablets were uncoated except for PN-1 and PN-2 which were film-coated. The tablet samples also passed the uniformity of weight determination except for PN-6. This implies that there was minimal variation or a fair distribution of the active pharmaceutical ingredient and excipients in each tablet manufactured. Identification test by melting point following extraction of the active ingredient from dosage forms revealed that melting point of the sample brands ranged between 94 and 99°C which conforms with the BP stated value. Further identification was also carried out by infrared spectroscopy. Propranolol consists of a number of functional groups which are essential for its identification using infrared (IR) spectroscopy. Table 3 shows some functional groups present in propranolol, their IR absorption frequency ranges, intensity, and the frequency from the spectra of each sample which tallies with normal frequency ranges. Notable functional groups obtained include hydroxyl, naphthyl ring, ether, and a secondary amino group.

Friability test results show that all but one brand passed the friability test as required by the BP. Thus, the brand most likely tolose particles during handling was brand PN-5, 1.52%, while the least likely to lose particles was brand PN-2, 0.21%. The hardness of a tablet is the crushing strength and it determines the ability of tablets to withstand the shock of handling without fracture or chipping and during transportation. It can also influence the friability and disintegration of tablets. The harder a tablet, the less friable and the more time it takes to disintegrate. It can be seen in Table 2 that brand PN-6 required the least pressure before fracture while brand PN-7 has the highest strength. A force of 4 kg/cm^2 is the minimum requirement for the hardness of a tablet[17]. Hence the tablets of all brands except PN-5 and PN-6 were satisfactory for hardness.

Disintegration can be linked to drug dissolution and consequently bioavailability of a drug. The active ingredient incorporated in a tablet matrix is released rapidly as the tablet disintegrates; a crucial step for immediate release dosage forms, because the rate of disintegration affects the dissolution and by extension the therapeutic efficacy of the medicine.

With regard to dissolution testing, there was a sharp release of the active pharmaceutical ingredient within 10 min after which release was sustained although gradual. All

the batches released more than 80% of their drug content within 30 min. Brand PN-3 exhibited a slightly greater release than others. However, all brands complied with the pharmacopoeial specifications in terms of their release pattern and can be said to appear similar as demonstrated in Figure 9.

For analysis of similarity factor, f_2 values for all brands except PN-7 were more than 50. Thus, they are similar to brand PN-1 and can be used interchangeably. For brand PN-7, f_2 value was less than 50 hence, it is not similar to brand PN-1 and cannot be used interchangeably.

CONCLUSION

The identification tests carried out for the batches of the tablet show the presence of propranolol hydrochloride. The assessment of mechanical strength and disintegration profile was found to be in accordance with compendial specifications except for PN-5 and PN-6. The content of active ingredients apart from PN-6 did not differ from the label claim for all the batches and these were found to comply with the BP standards. The dissolution profile showed all studied brands releasing up to 80 % of their active pharmaceutical ingredient within 30 min which complied with the BP and USP set limit. Thus, all brands of propranolol hydrochloride tablets evaluated except PN-5 and PN-6 can be adjudged to be pharmaceutical equivalents seeing that they fulfilled critical quality parameters.

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